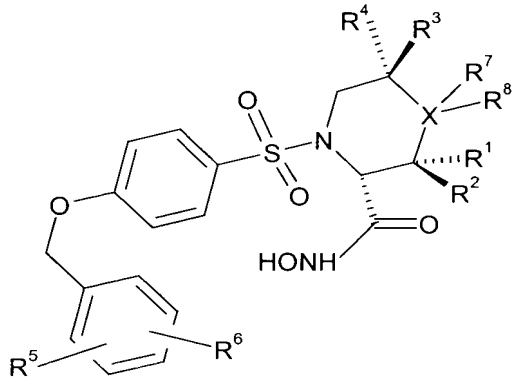
EXPRESS MAIL NO. EL162822485

SELECTIVE INHIBITION OF AGGRECANASE IN OSTEOARTHRITIS TREATMENT

Abstract

This invention relates to a method of treatment for osteoarthritis involving inhibitors of aggrecanase that demonstrate IC_{50}s of less than 20 nM and demonstrate differential potency against matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinases (ADAMs or reprolysins). This invention also relates to compounds, methods of treatment and composition of Formula I:



I

or a therapeutically acceptable salt thereof, wherein

X is carbon or nitrogen;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxy, and methyl, wherein at least one of R^1 and R^2 is methyl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxy, and methyl, or R^3 and R^4 may be taken together to form a carbonyl group; and

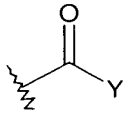
R^5 and R^6 are independent substituents in the ortho, meta, or para positions and are independently selected from the group consisting of hydrogen, halogen, cyano, methyl, and ethyl;

with the provisos:

when X is carbon, then R^7 and R^8 are both hydrogen and at least one of R^1, R^2, R^3, and R^4 is hydroxy;

when X is carbon and R^5 is para-halo, then at least one of R^6, R^3, and R^4 is not hydrogen;

when X is nitrogen, then R^8 is not present and R^7 is hydrogen or a group of the formula:



wherein, Y is $-CH_2-NH_2$ or $-NH-CH_3$; and

when X is nitrogen and R^7 is H, then R^3 and R^4 are taken together to form a carbonyl group.